UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,098	06/20/2003	Sean D. Monahan	Mirus. 013.03.2	7733

25032 7590 06/18/2007

MIRUS CORPORATION
505 SOUTH ROSA RD
MADISON, WI 53719

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
06/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,098	MONAHAN ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15-21 and 23-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13, 15-23, and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2003 and 19 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/600,098 was filed on June 20, 2003. As indicated in the first line of amended specification filed on 07/19/2004, this application is a divisional of non-provisional application US Serial No. 09/447,966, filed November 23, 1999, which is a Continuation-In-Part from non-provisional application 09/391,260, filed September 7, 1999, which is a Divisional from non-provisional application 08/975,573, issued as U.S. Patent 6,265,387, which is a Continuation from 08/571,536, filed December 13, 1995, abandoned.

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 02, 2007 has been entered.

Claims 1-12, 14, and 22 are canceled. Claims 13, 16, 26 and 27 have been amended.

Status of claims: Claims 13, 15-21 and 23-29 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous new matter rejection of claims 13, 15-21, and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is ***withdrawn*** because the claims have been amended.

Specifically, the amended claims 13 filed on 04/02/2007 no longer recites, "*analyzing the effects of expression of the gene on the cell*", and amended claim 16 filed on 04/02/2007 no longer recites, "*analyzing the effects of decreased expression of the gene on the cell*".

3. Previous rejection of claims 13, 15-21, and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is ***withdrawn*** because the claims have been amended.

Specifically, the amended claims 13 filed on 04/02/2007 no longer recites, "*analyzing the effects of expression of the gene on the cell*", and amended 16 filed on 04/02/2007 no longer recites, "*analyzing the effects of decreased expression of the gene on the cell*".

4. Claims 13, 15-21, and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 13, 15-21, and 23-29 fail to comply with the enablement requirement **(i)** because the applicants have amended **claim 13** to recite, "A process for *altering an endogenous property of an extravascular cell* comprising: injecting a naked polynucleotide encoding a gene into a blood vessel lumen, *in vivo*, and increasing permeability of the blood vessel, thereby delivering the naked polynucleotide to the extravascular cell outside of the blood vessel, wherein the gene is expressed; *thereby altering the endogenous property of the cell.*", and **(ii)** because the applicants have amended **claim 16** to recite, "A process for *delivering an oligonucleotide to an extravascular cell in a mammal* comprising: injecting a naked oligonucleotide into a blood vessel

lumen in the mammal, *in vivo*, and increasing permeability of the blood vessel thereby delivering the naked oligonucleotide to the extravascular cell outside of the blood vessel, wherein delivery of the oligonucleotide to the cell results in decreased expression of a gene." Claim 15 depends from claim 13 whereas claims 17-21 and 23-29 dependent from claim 16.

Claim 13 as amended requires a naked polynucleotide encoding a gene with the following characteristics: (1) the injection the naked polynucleotide encoding a gene can increase permeability of the blood vessel, and (2) the expression of the recited gene from the naked polynucleotide can deliver the said naked polynucleotide to an extravascular cell, and (3) the expression of the recited gene from the said naked polynucleotide can alter the endogenous property of the said extravascular cell.

Similarly, claim 16 as amended requires a naked oligonucleotide with the following characteristics: (1) the injection of the naked oligonucleotide can increase permeability of a blood vessel, and (2) the naked oligonucleotide can deliver itself to an extravascular cell, and (3) the delivery of naked oligonucleotide can decrease the expression of a gene in the said extravascular cell.

The specification provides information regarding polymers that when mixed with DNA can facilitate the delivery of the DNA molecule. Structures and synthesis of the polymers are presented in the Examples of the specification. However, the specification is totally silent on (i) a naked polynucleotide encoding a gene with abovementioned characteristics, and (ii) a naked oligonucleotide with abovementioned characteristics. More specifically, there is lack of enabling support in the specification regarding (i) a polynucleotide encoding a gene being injected into a blood vessel lumen and the expression of the gene after injection can not only deliver the

polynucleotide itself from the injected site to an extravascular cell but also alter the endogenous property of the said extravascular cell, and (ii) an oligonucleotide being injected into a blood vessel lumen can not only deliver the oligonucleotide itself from the injected site to an extravascular cell but also decrease the expression of a gene in the said extravascular cell.

In the absence of specific guidance or example, it will require undue experimentation for a skilled person in the art to figure out what kind of genes or oligonucleotides may fulfill the recited limitations in claim 13 and claim 16.

With regard to the aspect of administration of a polynucleotide encoding a gene thereby altering the endogenous property of the cell, as stated in claims 13 and 15, which encompass gene therapy, it is noted that while progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites has continued to be unpredictable and inefficient for the past decade. This statement is supported by numerous teachings available in the art. For example, **Pouton et al.** (Pouton and Seymour, Key issues in non-viral gene delivery, *Adv Drug Deliv Rev.* 46(1-3): 187-203, 2001) reviewed the issues in non-viral gene delivery and stated "direct injection of gene medicines into target tissue represents a far simpler task than targeting delivery to a specific tissue from the systemic circulation". See last full sentence on page 188, right column, and section 2.1. Pouton et al. added that there were "no systems yet available for efficient tissue targeting following systemic delivery." (See page 189, first sentence of section 2.2.). **Johnson-Saliba et al.** stated that although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches, especially when non-viral vectors are used, is the poor efficiency of DNA delivery to the nucleus; a crucial step to ensure ultimate

expression of the therapeutic gene product (See abstract, Johnson-Saliba et al. Gene therapy: optimizing DNA delivery to the nucleus. *Curr Drug Targets.* 2(4): 371-99, 2001). More recently, **Read et al.** (Read et al., Barriers to gene delivery using synthetic vectors, *Adv Genet.* 53: 19-46, 2005) stated after the time the invention was filed that the "lack of suitable vectors for the delivery of nucleic acids... represents a major hurdle to their continued development and therapeutic application" (see abstract, sentence bridging pages 19 and 20. Problem areas included obtaining persistence in the circulation, gaining access to target cells, and distinguishing target cells from non-target cells. See e.g. page 22). Finally, **Dobson** (Dobson, Gene therapy progress and prospects: magnetic nanoparticle-based gene delivery. *Gene Ther.* 13(4): 283-7, 2006) reviewed the development of non-viral transfection agents for gene delivery stated "While magnetic targeting appears to hold significant potential for gene therapy, there are still major obstacles to employing this technique in the clinic. Perhaps, the problem that is most difficult to overcome is, as with magnetic targeting for drug delivery, that of scale-up." (See Prospects on page 286).

With regard to the delivery of an oligonucleotide to a cell resulting in decreased expression of a gene as a approach of gene thearpy, which is encompassed by claims 16-21 and 23-29, **Shoji et al.** stated that the tragic failure of gene therapy resulted in rolling back the research of gene-based medicine. Because of the poor delivery of gene-based medicines, such as antisense oligonucleotides, ribozyme, triplex, or gene both *in vitro* and *in vivo*, further development of gene-based medicines as therapeutic agents have stagnated. Although the delivery system plays a critical role in the overall efficacy of oligonucleotides, inappropriate target selection, improper evaluation methods and misinterpretation of results often caused the

pessimistic view. Shoji et al. further stated delivery efficiency depends on the oligonucleotides' chemistry, length, size, net charge, cell/tissue type and administration route. It is difficult to deduce a common rule that affects delivery efficiency. Some cells like keratinocytes rapidly internalize oligonucleotides without a delivery system, which is contrary to common belief (See abstract, Shoji et al., Current status of delivery systems to improve target efficacy of oligonucleotides. *Current Pharmaceutical Design* 10(7): 785-96, 2004).

Therefore, there is a lack of predictability for an artisan to make and use of the claimed inventions. Additionally, it remains to be determined what the targeted extravascular cells are defined as. The specification teaches parenchymal cells are affected by the claimed methods. However, the claims encompass any cell outside the vasculature.

Therefore, there appears to be a lack of teachings in the specification connecting the information regarding polymers with functions in facilitating DNA delivery disclosed in specification, and the recited naked polynucleotide (claim 13) and oligonucleotide (claim 16) recited in the claims, and thereby an artisan cannot make and use the invention of a process for altering an endogenous property of an extravascular cell (claim 13) or a process for delivering an oligonucleotide to an extravascular cell in a mammal (claim 16).

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Previous rejection of claims 26 and 27 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because claim 26 and 27 have been amended.

Specifically, claims 26 and 27 are amended to depend from 16 instead claim 22, which was cancelled.

6. Previous rejection of claims 13, 15-21, and 23-29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because claim 13 and 16 have been amended.

Specifically, the amended claims 13 filed on 04/02/2007 no longer recites, "*analyzing the effects of expression of the gene on the cell*", and amended 16 filed on 04/02/2007 no longer recites, "*analyzing the effects of decreased expression of the gene on the cell*".

Conclusion

7. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
AU 1632

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632